mick.cooper@roehampton.ac.uk

ETHOS ADVERSE EVENTS INFORMATION DOCUMENT

1.1 Definitions

An adverse event (AE) is defined as any negative psychological, emotional or behavioural occurrence, or sustained deterioration in a research participant. These include:

- Arrest
- Running away from home
- Excluded from family home
- School exclusion (fixed term, or permanent exclusion)
- Significant decrease in school attendance
- Significant deterioration in behaviour, including threatening violence, exhibiting violent behaviour or serious injury to another person; or exposure to violence or abuse
- Significant increase in emotional difficulties
- Self-harm (if not a presenting issue), or escalating self-harm (when it is a presenting issue)
- A complaint made against the counsellor, or an issue with the counsellor, resulting in discontinuation of counselling
- Suicidal intent
- Hospitalization due to drugs or alcohol, or for psychiatric reasons
- Death, including suicide

AEs that occur and are not pre-defined above, are labelled 'other' with details provided and recorded according to the stipulations below.

A serious AE (SAE) is defined as any AE that is life-threatening, or results in death. Each AE must be classified as either a SAE or not a SAE on the Adverse Events Reporting Log (Appendix L6) (see section 13.5 of protocol). The only AEs which are known to be serious in advance of this assessment are suicidal intent and death (including suicide). All other AEs must be assessed on a case by case basis.

All SAEs qualify for expedited reporting (section 1.5.2) to the Data Monitoring and Ethics Committee (DMEC) and the Trial Steering Committee (TSC)

1.2 Causality of adverse events

AEs may occur during the course of being involved in the trial, in the context of SBHC, or may be caused by SBHC or PCAU. The ascertainment of a causal relationship between an AE and SBHC or PCAU is not possible on the basis of the occurrence of the AE alone, and must be assessed on a case by case basis. As part of the reporting procedures (see section 1.5), an attempt will be made by the individual reporting the AE, to establish causality using the following categories:

1. 'Related': a causal link between the event and SBHC or PCAU *cannot* be ruled out
2. 'Unrelated': a causal link between the event and SBHC or PCAU *can* be ruled out

Tester blinding will be maintained during the process of assessing the causality of the AE, by asking young people to complete measures before any discussion of the occurrence of an AE. In addition, to help ensure the success of the blind, a different Tester will be employed at midpoint, endpoint and follow-up for each participant (see section 10.1 of protocol).

AEs considered to be related by SBHC or PCAU qualify for expedited reporting (section 1.5.2) to the DMEC and TSC.

1.3 Assessing the severity of an adverse event

The severity of each AE will also be assessed, according its intensity, duration and the degree of impairment to the young person (or, when relevant, another person such as in case of risk to others). Severity will be graded as either 'mild', 'moderate', 'severe', 'very severe', or 'extremely severe' (Linden &

mick.cooper@roehampton.ac.uk

Schermuly-Haupt, 2014) as part of the reporting procedures (see section 15.5). The severity is only known in advance for three pre-defined AEs: suicidal intent, hospitalization, and death (including suicide) which are all graded as 'very severe' or 'extremely severe'. The severity of any other AE must be assessed on a case by case basis.

AEs assessed as severe, very severe or extremely severe should be reported to the CI immediately, but no later than two working days of becoming aware of the event. The CI may consider reporting the AE to the DMEC via expedited reporting depending on the outcome of his own assessment (see section 1.7).

1.4 Detecting AEs

AEs may be measured subjectively and objectively. Subjective measurement includes the young person's perception of the effect of the AE on self and on others, and is disclosed by the young person to an Assessor, their Counsellor, a Tester, an Interviewer, or a member of the pastoral care team. Objective reporting involves an observation made of the young person by an Assessor, their Counsellor, the Counsellor's Supervisor, a Tester, an Interviewer, or a member of school staff. Objective reporting is the responsibility of these individuals, who will be required to make on-going assessments of risk of AEs using the aforementioned definitions (section 1.1).

The time period for detecting AEs is from the point at which the young person is considered eligible to take part in the trial, to the follow-up time point (24 weeks post baseline). For those young people not receiving SBHC (either because they have been allocated to PCAU, or because they have been allocated to SBHC but are no longer receiving counselling), pastoral care staff will be responsible for detecting AEs.

The occurrence of AEs will constitute a standing agenda item in every supervision session the Counsellor attends. The Supervisor, together with the Counsellor, will also review the number of participants, within the Counsellors' case load, who end their counselling before 10 sessions and consider any potential link between issues the participant and the Counsellor experienced working together and the ending of the counselling (see section 11.4 of protocol for further details on supervision of counsellors).

1.5 Reporting Procedures

The overall safety of participants is the responsibility of the CI. However, in practice the CI must rely on all research staff, Counsellors, Supervisors and school staff to ensure that AEs are identified and addressed in an appropriate and timely manner. Thus, safety is a shared responsibility. The procedures for reporting AEs are outlined in Figure 3.

1.5.1 AE Reporting Log

All AEs that occur between the point at which the young person is considered eligible to take part in the trial, and the follow-up time point (24 weeks post baseline) must be recorded in the AE Reporting Log (Appendix L6). Details on what information is required includes:

- Participant ID
- Name and role of the professional reporting the AE
- The AE itself
- Whether the event is considered a SAE (Yes or No)
- An assessment of causality (Related or Unrelated)
- An assessment of severity (mild, moderate, severe, very severe, or extremely severe)
- Expedited reporting necessary (Yes or No)
- Date AE detected
- Date AE resolved
- Action(s) taken as they relate to the participant's involvement with the trial (participation continues or participant withdrawn)
- Action(s) taken as they relate to the involvement of other professionals (reported to CI; expedited reporting considered necessary; reported to pastoral care team member, reported to school's Child Protection Officer)

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The AE Reporting Log will be electronically filed securely, using password protection. All sections of the AE Reporting Log should be completed. The occurrence of any AE will be reported to the CI via a dedicated email address within five working days. For details regarding the reporting process for SAEs and AEs assessed as related to SBHC or PCAU see section 1.5.2 ('Expedited reporting'). In cases of severe, very severe of extremely severe AEs, the AE Reporting Log should be reported to the CI immediately, but no later than two working days of becoming aware of the event, marking the email 'high priority' and making a phone call to the CI leaving a message if the CI is unavailable.

It is the responsibility of the CI to review the AE Reporting Logs at least monthly, and in instances of severe, very severe or extremely severe AEs, the AE Reporting Log should be reviewed immediately.

In cases where the AE raises a child protection issue, the school's usual child protection protocol will be observed. The protection and safety of the young person is of paramount importance and therefore in cases where the AE does raise a child protection issue, the child protection issue must be dealt with first, before the AE Reporting Log is emailed to the CI. This process should also be observed in cases of expedited reporting.

1.5.2 Expedited reporting

Any AE assessed as related to SBHC or PCAU, *or* classified as a SAE qualifies for expedited reporting to the DMEC and TSC.

The individual who has detected the AE or SAE is responsible for reporting it to the CI immediately, but no later than two working days of becoming aware of the event, by sending an email marked 'high priority' and making a phone call to the CI leaving a message if the CI is unavailable.

The CI is then responsible for reporting the AE or SAE to the Chair of the DMEC immediately, but no later than 1 working day of receiving the AE Reporting Log. The Chair of the DMEC must notifying the Chair of the TSC, and make recommendations regarding trial continuation or termination. It is the responsibility of the TSC to then consider the implications of the AE to trial safety on the basis of the DMEC's recommendations, with respect to continuation or termination (see section 16.1 of protocol).

mick.cooper@roehampton.ac.uk

All AEs assessed as **related to SBHC or PCAU** or **classified as a SAE** must be reported to the CI by sending an email marked high priority, with the completed AE Reporting Log, immediately, but no later than 2 working days of becoming aware of the event to the ETHOS CI at the University of Roehampton:

[dedicated email address]

A phone call should also be made, leaving a message if the CI is unavailable:

[dedicated phone number]

1.6 Management of the AE Reporting Log

It is the responsibility of the individual reporting an AE to email the AE Reporting Log to the CI. It is the responsibility of the CI to ensure all relevant parties are informed of the occurrence of an AE, as it is recorded in the AE Reporting Log. These include: the DMEC, the TSC and MAHSC-CTU.

It is the responsibility of the CI (or designated nominee, usually the PM) to provide MAHSC-CTU with copies of the AE Reporting Log for data input. MAHSC-CTU will provide safety data to the DMEC as part of the reports they prepare prior to DMEC meetings (see section 16.2). The Chair of the DMEC is responsible for providing safety reports to the TSC (see section 16.2).

Normal reporting procedure:

Individual reports AE → CI → MAHSC-CTU → DMEC → TSC

In instances of an AE assessed as related to SBHC, or classified as an SAE, the CI must inform the DMEC immediately, but no later than one working day of receiving the AE Reporting Log. In these instances it is then the responsibility of the Chair of the DMEC to notify the Chair of the TSC immediately, but no later than one working day of receiving the AE Reporting Log from the CI. It is the responsibility of the DMEC to make recommendations to the TSC regarding trial continuation or termination. It is the responsibility of the TSC to consider the implications of the AE, as it has been recorded in the AE Reporting Log, regarding trial safety with respect to continuation or termination (see sections 16.1 of protocol).

In such cases, the CI will inform MAHSC-CTU of the steps needed to be undertaken as part of expedited reporting procedures. Copies of the AE Reporting Log will be provided to MAHSC-CTU for data input as normal.

Expedited reporting procedure:

Individual reports AE → CI → DMEC → TSC

On receipt of the AE Reporting Log, the CI (or designated nominee, usually the PM) will send an acknowledgement to the individual who reported the AE. This acknowledgement will include an AE reference number which should be included on all future correspondence regarding the AE. In instances of an AE assessed as related to SBHC, or classified as an SAE, acknowledgement must be emailed immediately, but no later than 1 working day after receipt. The CI (or designated nominee, usually the PM) will then be required to review, and sign-off, the assessment of causality and severity attributed to the AE reported (see section 1.7).

mick.cooper@roehampton.ac.uk

1.7 Review and resolution of adverse events

The CI will be required to review the assessments of causality, seriousness and severity attributed to the AE reported and assign their own judgment. To do this, the CI needs to: (1) review the event itself and the actions taken; and (2) in the case of the AE occurring in a participant allocated to SBHC group, review the number of sessions the young person has had, and the date of their last session. The CI will also be required to provide sign-off on final assessments of causality, seriousness and severity and email this to the individual who reported the AE.

In certain circumstances, the CI will need to hold a meeting with the professional who filed the AE Reporting Log (including the Counsellor and their Supervisor in cases of the AE occurring in a young person allocated to SBHC), to collaboratively identify potential causality and establish seriousness and severity. These instances include:

1. Where there is a difference of opinion regarding causality, seriousness or severity of an AE
2. When a significant number of AEs are reported at a single school

In cases where differences of opinion regarding causality are difficult to resolve during this meeting, the view of the Counsellor, Supervisor or pastoral care team member is assumed, as they will be more familiar with the participant's history and current issues.

If differences in opinion in the seriousness or severity grade are difficult to resolve during this meeting, the 'worst-case' assessment is assumed.

If the outcome of this meeting changes the original assessment of the AE, and the AE is reclassified as a SAE, or as related to SBHC or PCAU, expedited reporting procedures should be adhered to (see section 1.5.2 and 1.6).

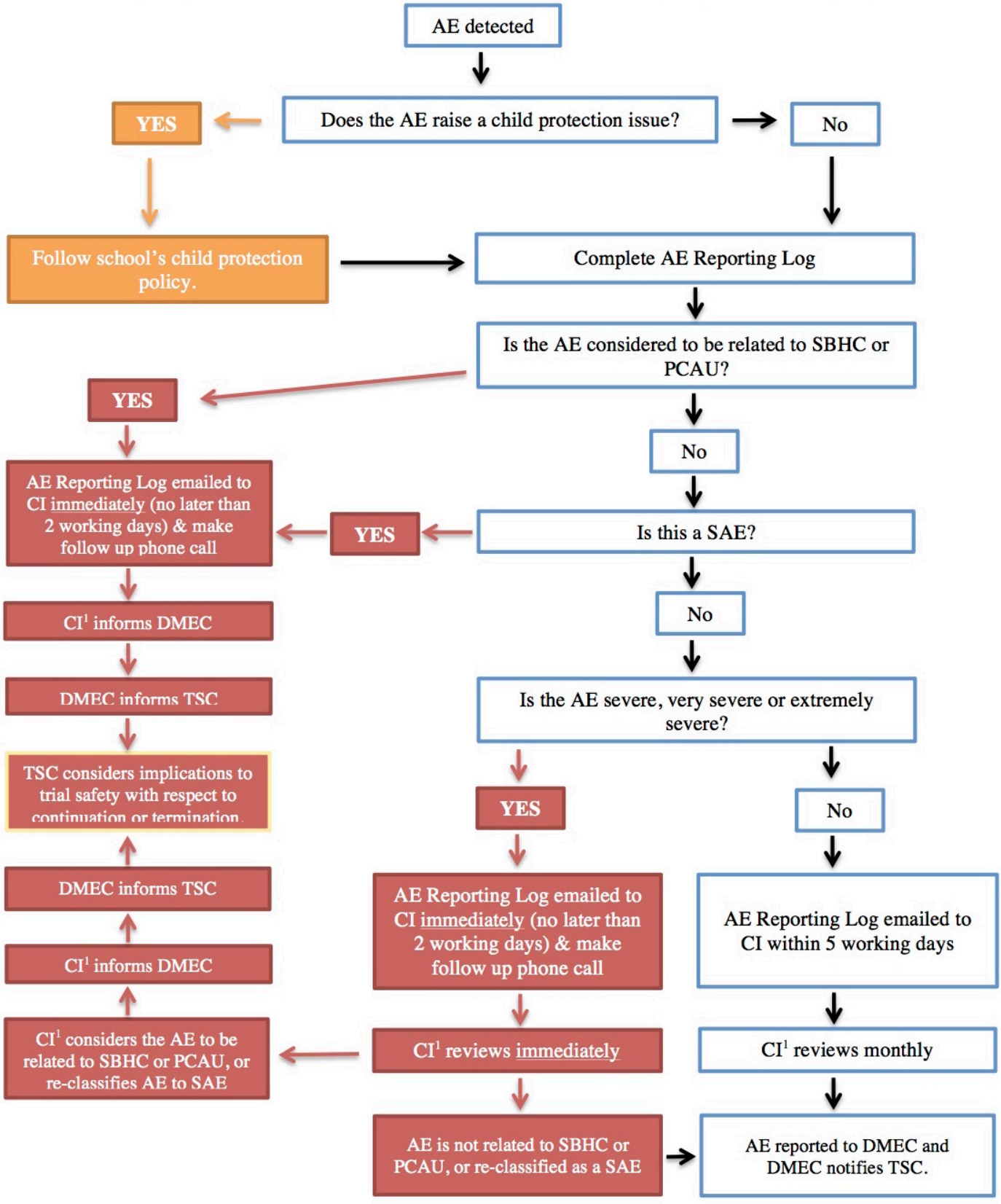
All AEs will be monitored by the Counsellor until resolution, or for those young people not receiving SBHC (either because they have been allocated to PCAU, or because they have been allocated to SBHC but are no longer receiving counselling), pastoral care staff will be responsible for monitoring the AE until resolution. The CI is responsible for ensuring pastoral care staff are aware of any unresolved AEs at the point of follow-up (24 weeks post baseline).

1.8 New Safety Findings

If new findings regarding the safety of SBHC emerge, the CI will review the findings for their impact on the participants in the ETHOS study. If there is a potential impact on trial participant's safety, the appropriate action will be taken by the research team. Appropriate reporting mechanisms are followed in the event of actions being taken.

mick.cooper@roehampton.ac.uk

Figure 3: Procedures for Reporting and Resolving Adverse Events (AEs)



[1]Summary of CI responsibilities

- Communicating to the DMEC (DMEC communicates to the TSC)
- On receipt of AE Reporting Log, the CI must:
  - Review assessments of causality, seriousness and severity
  - Consider number of AEs occurring per school
  - Hold a meeting with professional who reported AE when appropriate